Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1 (currently amended): A nucleic acid-lipid particle composition for introducing a nucleic acid into a cell, said particle composition comprising:

(a) a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a nucleic acid, wherein said nucleic acid is encapsulated in the lipid, and wherein said conjugated lipid that inhibits aggregation of particles is a member selected from the group consisting of a PEG-lipid, an ATTA-lipid and a cationic-polymer-lipid conjugate having the formula

A—W—Y

I

wherein:

A is a lipid moiety;

W is a hydrophilic polymer; and

Y is a polycationic moiety; and

(b) an endosomal membrane destabilizer, wherein said endosomal membrane destabilizer is Ca^{++} ion.

2 (original): The nucleic acid-lipid particle composition of claim 1, wherein said endosomal membrane destabilizer is outside said nucleic acid-lipid particle.

3 (original) The nucleic acid-lipid particle composition of claim 1, wherein said endosomal membrane destabilizer is both outside and inside said nucleic acid-lipid particle.

4 (cancelled)

5 (withdrawn): The nucleic acid-lipid particle composition of claim 4, wherein the concentration of Ca^{++} ion is from about 0.1 mM to about 100 mM.

6 (original): The nucleic acid-lipid particle composition of claim 5, wherein the concentration of Ca^{++} ion is from about 1 mM to about 20 mM.

7 (original): The nucleic acid-lipid particle composition of claim 1, wherein said particle has a median diameter of less than about 150 nm.

8 (original): The nucleic acid-lipid particle composition of claim 1, wherein said cationic lipid is a member selected from the group consisting of N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), and N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), and combinations thereof.

9 (original): The nucleic acid-lipid particle composition of claim 1, wherein said particle further comprises an additional noncationic lipid.

10 (original): The nucleic acid-lipid particle composition of claim 9, wherein said noncationic lipid is selected from the group consisting of DOPE, POPC, and EPC.

11 (original): The nucleic acid-lipid particle composition of claim 1, wherein said particle comprises a functional group that facilitates Ca^{++} ion chelation.

12 (original): The nucleic acid-lipid particle composition of claim 1, wherein said conjugated lipid that inhibits aggregation of particles has the formula

A——W——Y

I

wherein:

A is a lipid moiety;

W is a hydrophilic polymer; and

Y is a polycationic moiety.

13 (original): The nucleic acid-lipid particle composition of claim 12, wherein W is a polymer selected from the group consisting of PEG, polyamide, polylactic acid, polyglycolic acid, polylactic acid/polyglycolic acid copolymers and combinations thereof, said polymer having a molecular weight of about 250 to about 7000 daltons.

14 (original): The nucleic acid-lipid particle composition of claim 12, wherein Y has at least 4 positive charges at a selected pH.

15 (original): The nucleic acid-lipid particle composition of claim 12, wherein Y is a member selected from the group consisting of lysine, arginine, asparagine, glutamine, derivatives thereof and combinations thereof.

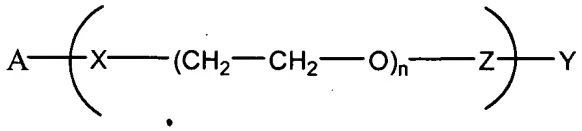
16 (original): The nucleic acid-lipid particle composition of claim 12, wherein A is a member selected from the group consisting of a diacylglycerolyl moiety, a dialkylglycerolyl moiety, a N-N-dialkylamino moiety, a 1,2-diacyloxy-3-aminopropane moiety and a 1,2-dialkyl-3-aminopropane moiety.

17 (original): The nucleic acid-lipid particle composition of claim 12, wherein W is PEG.

18 (withdrawn): The nucleic acid-lipid particle composition of claim 12, wherein W is a polyamide polymer.

19 (original): The nucleic acid-lipid particle composition of claim 12, wherein W has a molecular weight of about 250 to about 2000 daltons.

20 (original): The nucleic acid-lipid particle composition of claim 17, having the general structure of Formula II:



II

wherein

X is a member selected from the group consisting of a single bond or a functional group covalently attaching said lipid to at least one ethylene oxide unit;

Z is a member selected from the group consisting of a single bond or a functional group covalently attaching said at least one ethylene oxide unit to a cationic group; and

n is an integer having a value of between about 6 to about 50.

21 (original): The nucleic acid-lipid particle composition of claim 20, wherein

X is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

22 (original): The nucleic acid-lipid particle composition of claim 20, wherein

Z is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

23 (original): The nucleic acid-lipid particle composition of claim 20, wherein

A is a diacylglycerolyl moiety;

X is phosphoethanolamido;

Z is NR, wherein R is a hydrogen atom; and

Y is a member selected from the group consisting of about 1 to about 10 basic amino acids or derivatives thereof.

24 (original): The nucleic acid-lipid particle composition of claim 23, wherein A is a diacylgercerolyl moiety having 2 fatty acyl chains, wherein each acyl chain is independently between 2 and 30 carbons in length and is either saturated or has varying degrees of saturation.

25 (original): The nucleic acid-lipid particle composition of claim 23, wherein Y is a member selected from the group consisting of lysine, arginine, asparagine, glutamine, derivatives thereof and combinations thereof.

26 (original): The nucleic acid-lipid particle composition of claim 23, wherein A is a diacylgercerolyl moiety having 2 fatty acyl chains, wherein each acyl chain is a saturated C-18 carbon chain; and
Y is a cationic group having 4 lysine residues or derivatives thereof.

27 (original): The nucleic acid-lipid particle composition of claim 1, wherein said conjugated lipid that inhibits aggregation of particles is a PEG-lipid.

28 (original): The nucleic acid-lipid particle composition of claim 27, wherein said PEG-lipid is PEG-ceramide.

29 (original): The nucleic acid-lipid particle composition of claim 28, wherein the ceramide of said PEG-ceramide comprises a fatty acid group having about 8 to about 20 carbon atoms.

30 (original): The nucleic acid-lipid particle composition of claim 28,wherein said PEG-lipid is PEG-phosphatidylethanolamine.

31 (withdrawn): The nucleic acid-lipid particle composition of claim 1, wherein said conjugated lipid that inhibits aggregation of particles is an ATTA-lipid.

32 (original): The nucleic acid-lipid particle composition of claim 1, wherein said nucleic acid is selected from the group consisting of a plasmid, an antisense oligonucleotide, and a ribozyme.

33 (currently amended): A method of introducing a nucleic acid into a cell, said method comprising:

contacting said cell with a nucleic acid-lipid particle composition, said particle composition comprising:

(a) a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a nucleic acid, wherein said nucleic acid is encapsulated in the lipid, and wherein said conjugated lipid that inhibits aggregation of particles is a member selected from the group consisting of a PEG-lipid, an ATTA-lipid and a cationic-polymer-lipid conjugate having the formula

A——W——Y

I

wherein:

A is a lipid moiety;

W is a hydrophilic polymer; and

Y is a polycationic moiety; and

(b) an endosomal membrane destabilizer, wherein said endosomal membrane destabilizer is Ca^{++} ion.

34 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said endosomal membrane destabilizer is outside said nucleic acid-lipid particle.

35 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said endosomal membrane destabilizer is Ca^{++} ion.

36 (withdrawn): The method of introducing a nucleic acid into a cell of claim 35, wherein the concentration of Ca^{++} ion is from about 0.1 mM to about 100 mM.

37 (original): The method of introducing a nucleic acid into a cell of claim 36, wherein the concentration of Ca^{++} ion is from about 1 mM to about 20 mM.

38 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said particle has a median diameter of less than about 150 nm.

39 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said cationic lipid is a member selected from the group consisting of N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), and N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), and combinations thereof.

40 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said particle further comprises an additional noncationic lipid.

41 (original): The method of introducing a nucleic acid into a cell of claim 40, wherein said noncationic lipid is selected from the group consisting of DOPE, POPC, and EPC.

42 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said particle comprises a functional group that facilitates Ca^{++} ion chelation.

43 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said conjugated lipid that inhibits aggregation of particles has the formula

A——W——Y

I

wherein:

A is a lipid moiety;

W is a hydrophilic polymer; and

Y is a polycationic moiety.

44 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W is a polymer selected from the group consisting of PEG, polyamide, polylactic acid, polyglycolic acid, polylactic acid/polyglycolic acid copolymers and combinations thereof, said polymer having a molecular weight of about 250 to about 7000 daltons.

45 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein Y has at least 4 positive charges at a selected pH.

46 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein Y is a member selected from the group consisting of lysine, arginine, asparagine, glutamine, derivatives thereof and combinations thereof.

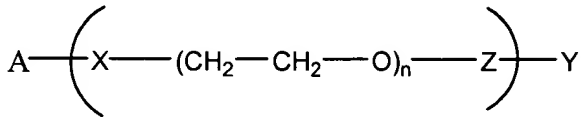
47 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein A is a member selected from the group consisting of a diacylglycerolyl moiety, a dialkylglycerolyl moiety, a N-N-dialkylamino moiety, a 1,2-diacyloxy-3-aminopropane moiety and a 1,2-dialkyl-3-aminopropane moiety.

48 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W is PEG.

49 (withdrawn): The method of introducing a nucleic acid into a cell of claim 43, wherein W is a polyamide polymer.

50 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W has a molecular weight of about 250 to about 2000 daltons.

51 (original): The method of introducing a nucleic acid into a cell of claim 48, having the general structure of Formula II:



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wherein

X is a member selected from the group consisting of a single bond or a functional group covalently attaching said lipid to at least one ethylene oxide unit;

Z is a member selected from the group consisting of a single bond or a functional group covalently attaching said at least one ethylene oxide unit to a cationic group; and

n is an integer having a value of between about 6 to about 50.

52 (original): The method of introducing a nucleic acid into a cell of claim 51, wherein

X is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

53 (original): The method of introducing a nucleic acid into a cell of claim 51, wherein

Z is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

54 (original): The method of introducing a nucleic acid into a cell of claim 51, wherein

A is a diacylglycerolyl moiety;

X is phosphoethanolamido;

Z is NR, wherein R is a hydrogen atom; and

Y is a member selected from the group consisting of about 1 to about 10 basic amino acids or derivatives thereof.

55 (original): The method of introducing a nucleic acid into a cell of claim 54, wherein

A is a diacylgercerolyl moiety having 2 fatty acyl chains, wherein each acyl chain is independently between 2 and 30 carbons in length and is either saturated or has varying degrees of saturation.

56 (original): The method of introducing a nucleic acid into a cell of claim 54, wherein

Y is a member selected from the group consisting of lysine, arginine, asparagine, glutamine, derivatives thereof and combinations thereof.

57 (original): The method of introducing a nucleic acid into a cell of claim 54, wherein

A is a diacylgercerolyl moiety having 2 fatty acyl chains, wherein each acyl chain is a saturated C-18 carbon chain; and

Y is a cationic group having 4 lysine residues or derivatives thereof.

58 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said conjugated lipid that inhibits aggregation of particles is a PEG-lipid.

59 (original): The method of introducing a nucleic acid into a cell of claim 58, wherein said PEG-lipid is PEG-ceramide.

60 (original): The method of introducing a nucleic acid into a cell of claim 59, wherein the ceramide of said PEG-ceramide comprises a fatty acid group having about 8 to about 20 carbon atoms.

61 (original): The method of introducing a nucleic acid into a cell of claim 59, wherein said PEG-lipid is PEG-phosphatidylethanolamine.

62 (withdrawn): The method of introducing a nucleic acid into a cell of claim 33, wherein said conjugated lipid that inhibits aggregation of particles is an ATTA-lipid.

63 (original): The method of introducing a nucleic acid into a cell of claim 33, wherein said nucleic acid is selected from the group consisting of a plasmid, an antisense oligonucleotide, and a ribozyme.

64 (withdrawn): A method for inducing H_{II} phase structure in a lipid bilayer, said method comprising: contacting said lipid bilayer with an endosomal membrane destabilizer, thereby inducing H_{II} phase structure in a lipid bilayer.

65 (withdrawn): The method for inducing H_{II} phase structure of claim 64, wherein said lipid bilayer comprises DOPC:DOPE:DOPS:Chol.

66 (withdrawn): The method for inducing H_{II} phase structure of claim 64, wherein said endosomal membrane destabilizer is Ca^{++} ion.

67 (withdrawn): The method for inducing H_{II} phase structure of claim 66, wherein Ca^{++} ion acts in concert with low levels of the cationic lipid to trigger H_{II} phase formation.

68 (cancelled)